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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20031120

Application Number: 09/881,635
Filing Date: June 14, 2001
Appellant(s): PRICE ET AL.

Benjamin Aaron Adler
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/22/2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because claims 1, 3 and 5 are drawn to a method of treating or preventing a

pathophysiological state of a kidney, while claim 6 and 8 are drawn to a method for treating or preventing chronic progressive renal failure. It is noted that a method of treating or preventing a pathophysiological state of a kidney is a genus that includes treating or preventing any pathophysiological state of the kidney, including chronic renal failure (claims 6 and 8). The rejection under 35 U.S.C. 112, first paragraph is appropriate for the genus claims as well as all species claims. Therefore, all claims should stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) References of Record

RG Crystal, "Transfer of Genes to Humans; Early Lessons and Obstacles to Success," Science, Oct. 1995, Vol. 270, pp. 404-410.

IM Verma et al., "Gene therapy-promises, problems and prospects." Nature, Sept. 1997. Vol. 389, pp 239-242.

AD Branch, "A good antisense molecule is hard to find." TIBS, Feb 1998, pp 45-50.

AK Khanna et al., "Cyclosporine Induces the Expression of the Cyclin Inhibitor p21" Transplantation, May 1999, Vol. 67, No. 9, pp 1262-1268.

DM Harlan et al., "The Future of Organ and Tissue Transplantation," JAMA, Sep. 1999, Vol. 282, No. 11, pp. 1076-1082.

W Walther et al., "Viral Vectors for Gene Transfer," Drugs, Aug. 2000, 60:2, pp. 249-271.

GP Dotto, "p21(WAF1/CIP1): more than a break in the cell cycle?" Biochimica et Biophysica Acta, 200, Vol. 1471, pp. M43-M56.

AM el Nahas et al., "Renal fibrosis: insights into pathogenesis and treatment." International Journal of Biochemistry and Cell Biology, 1997, Vol. 29, pp. 55-62.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 3, 5, 6 and 8 are rejected under 35 U.S.C. 112, first paragraph, for containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The grounds of this rejection can be found in prior Office Action Paper No. 9 (Final Rejection, mailed 1/14/2003) and, for convenience, is reproduced below.

The claims are drawn to a method for treating or preventing a pathological state of the kidney in an individual wherein said state is characterized by an undesirable level of cyclin-

dependent kinase inhibitor activity in the kidney, wherein the method comprises the step of reducing or eliminating the expression of the p21 gene in said kidney of said individual. The amendment limits the scope of the claims to treating or preventing a pathological state of a kidney by reducing or eliminating the expression of the p21 gene. However, the claims still contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons set forth in the previous Office Action.

The claims are still very broad and encompass treating or preventing any pathological state of a kidney by reducing or preventing the expression of the p21 gene in the kidney. Therefore, the broadest claims encompass treating or preventing renal fibrosis, glomerulosclerosis, reduced filtration rates, hypertension, rejection of kidney transplants, kidney cancer, etc. Furthermore, the method encompasses reducing or eliminating the expression the p21 gene by administering any compound that reduces or eliminates p21 gene expression. Therefore, the broadest claims encompass administering a broad genus of therapeutic agents including a gene therapy construct that expresses an inhibitor of p21 expression, antisense molecules which inhibit the translation of p21, chemical compounds which reduce the expression of the p21 gene, etc.

As mentioned in the previous Office Action, the relevant art considered gene therapy and antisense therapy methods to be unpredictable, and regarding treating organ transplant rejection, the relevant prior art contemplates increasing p21 expression to treat organ transplant rejection—not decreasing p21 expression, as contemplated by the instant application (see previous Office Action, p. 6 second paragraph). It was also noted that there are no working examples in the

specification indicating that reducing or eliminating p21 expression would have any therapeutic effect on any pathophysiological state of the kidney. It was also noted that the specification indicates that transgenic mice which do not express p21 (i.e. p21 knock-out mice) were resistant to the functional and morphologic consequences of partial renal ablation. However, there are no working examples or guidance indicating that an animal which expresses p21 can be administered any therapeutic molecule to reduce or eliminate p21 expression in the animal. No known molecules have been identified which could be administered to an animal and completely eliminate the expression of any gene. Furthermore, the specification does not specifically indicate any such molecules other than to merely state, "reduction or elimination of p21 expression is performed by techniques such as drug therapy, genetic manipulation, or antisense DNA, etc." (See p. 9, lines 8-10 of the specification).

Considering the breadth of the claims and the lack of working examples or guidance in the specification, the quantity of experimentation in this area is considered to be extremely large since determination of the efficacy of treatment would require, initially, the identification of therapeutic molecules in animal models. Gene therapy, antisense therapy, and other therapeutic molecules would have to be produced and tested in animals for efficacy. This would require making and testing the therapeutic molecules and testing the therapeutic molecules in vitro, followed by testing in animal models to show that the treatment can overcome the problems recognized in the art (mentioned above, and in the previous Office Action). Therefore for the reasons mentioned above and the reasons set forth in the previous Office Action, the amount of additional experimentation required to make and use the invention is considered to be undue.

(11) Response to Argument

The Appellant correctly states the Examiner's position that the claimed methods for treating a pathological state of the kidney in an individual by reducing or eliminating the expression of the p21 gene are not supported by the specification so as to enable one skilled in the art to make and/or use the invention, and that the relevant issues are: 1) that kidney disorders involve many different mechanisms, so that reducing or eliminating p21 may not treat every kidney disorder encompassed by the claims; 2) the p21 knock-out mouse is not a proper model for the claimed therapy; and 3) methods to efficiently reduce or eliminate p21 expression in a kidney are unpredictable such that an undue amount of experimentation is required in order to perform the claimed methods (See page 7 of the Appeal Brief).

The Appellant argues that the specification discloses experiments employing partial renal ablation as a model of chronic renal failure from diverse causes (See page 8 of the Appeal Brief). For example, it is indicated that mice expressing a homozygous null mutation in p21 are clearly demonstrated to be highly resistant to the deleterious effects of partial renal ablation, and removal of p21 expression allowed the growth response in the kidney after partial ablation to be relatively more hyperplastic than in controls, so that the kidney work-load was then better accommodated by the increased growth (See page 8 of the Appeal Brief).

In response, it is respectfully pointed out that the experiments disclosed in the specification utilize mice that have been genetically engineered such that the mice do not express the p21 gene (i.e., p21 knock-out mice). The claims encompass treating or preventing a pathophysiological state of a kidney in an individual comprising the step of reducing or eliminating the expression of the p21 gene in said kidney of said individual. Therefore, the

claims require that: 1) the individual **MUST** express p21, and 2) the expression of p21 **MUST** be reduced or eliminated. An appropriate animal model would express p21 in its kidney cells, and could be used to test potential therapeutic molecules for their ability to reduce or eliminate p21 expression in the animal. The genetically engineered mice used in the experiments described in the specification (i.e., p21 knockout mice) are not appropriate animal models for the claimed invention because they do note express the p21 gene at anytime in their lives, as required by the claims.

Furthermore, the genetically engineered mice used in the experiments described in the specification are not appropriate animal models for drug therapy or genetic manipulation (i.e. gene therapy or antisense therapy) because the methods used to eliminate p21 expression in the experiments presented in the specification are fundamentally different from the claimed methods. Specifically, the mice used in the experiments described in the specification have been genetically engineered using site directed homologous recombination to disrupt the p21 gene in a mouse embryonic stem cell. This genetically altered cell was then used to create a mouse that does not express p21 in any of its cells. The claimed methods encompass reducing or eliminating p21 expression in kidney cells using methods such as drug therapy, gene therapy and antisense therapy. However, methods of genetic manipulation (i.e., gene therapy and antisense therapy) were not a matter of routine experimentation at the time of filing, nor are they currently considered a matter of routine experimentation, as indicated in the previous Office Action. The mouse model used in the described experiments does not address the problems associated with reducing or eliminating p21 gene expression using gene therapy or antisense therapy. For example, delivery of the genetic material to the appropriate target cell, protection of the genetic

material from degradation by nucleases, and proper expression of the molecules of interest (i.e., the therapeutic protein or the therapeutic antisense molecules) are some problems that must be addressed for successful gene therapy and antisense therapy. The experiments presented in the specification do not address these problems and have not offered any guidance on how to overcome these art-recognized problems.

Furthermore, the specification does not teach on of skill in the art how to eliminate p21 expression in subject using genetic manipulation. The term "genetic manipulation" encompasses gene therapy as well as antisense therapy. As previously mentioned, the relevant art considers gene therapy and antisense therapy methods to be unpredictable. Gene therapy, as it pertains to the instant case, involves administering a nucleic acid which expresses a protein that reduces or eliminates p21 gene expression, while antisense therapy encompasses administering antisense nucleic acid molecules (or a vector which produces the antisense molecules) that specifically hybridize to target mRNA molecules (in this case p21 mRNA molecules) and reduces or eliminates expression of the target mRNA molecules. Drug therapy encompasses the administration of drugs (i.e. chemical molecules) that specifically reduce or eliminates the expression of the p21 gene. The specification does not describe any of the chemical molecules which can be used in the "drug therapy" methods, nor has the specification described any methods of using the drugs to reduce or eliminate p21 expression in kidneys. Regarding gene therapy, in order to practice the claimed method, the specification would have to instruct one of skill in the art how to administer a nucleic acid encoding a protein that reduces or eliminates expression of p21 in a subject such that the administration overcomes the art-recognized recognized problems associated with gene therapy. In the instant case, the specification does not

describe any nucleic acids which encode a protein that reduces or eliminates expression of p21, nor is there any guidance provided in the specification to overcome the art-recognized problems associated with gene therapy. Regarding antisense therapy, the specification does not provide guidance to overcome the art-recognized problems associated with antisense therapy.

Therefore, the specification does not provide any guidance or working examples that would teach one of skill in the art on how to reduced or eliminate p21 expression in a kidney (or kidneys) using drug therapy or genetic manipulation. Without any guidance, one of skill in the art would not know how to overcome the problems associated with drug therapy and genetic manipulation without performing an undue amount of additional experimentation.

Additionally, the claims encompass treating or preventing a pathophysiological state of a kidney by **REDUCING** or eliminating p21 expression in the kidney of the individual. It is noted that reducing p21 expression encompasses lowering but not eliminating p21 expression in the target cells of the individual. The animals used in the described experiments do not at any time in their lives express p21 in their kidneys; therefore, they are inappropriate animal models for treating or preventing a pathophysiological state of a kidney by **REDUCING** p21 expression. Furthermore, there is no evidence presented that merely reducing p21 expression, but not eliminating p21 expression, would have any beneficial effect.

Appellant submits that given the degree of experimentation that is routine in the art of regulation of gene expression, the amount of experimentation required of one skilled in the art to practice the claimed methods is not undue (See the last paragraph on page 10 of the Appeal Brief). Applicant assert that the disclosures of the present specification, coupled with the

knowledge of one skilled in the art at the time of filing, enables one so skilled to practice the claimed invention without undue experimentation (See paragraph bridging pages 11-12 of the Appeal Brief). Applicant submits that there was ongoing research and development of gene therapy and antisense methods at the time of filing of the present application. The Appellant cites Crystal (Science 270:404-410 (1995)) as stating that enough information has been gained from clinical trials to allow the conclusion that human gene transfer is feasible, can evoke biological responses that are relevant to human disease, and adverse events have been uncommon and have been related to the gene delivery strategies, not to the genetic material being transferred. The Appellant cites a specific quotation from Crystal: "Taken together, the evidence is overwhelming, with successful human gene transfer having been demonstrated in 28 ex vivo and 10 in vivo studies" (Crystal, page 405, third column, second paragraph; Tables 1 and 2; See page 12 of the Appeal Brief).

In response, it is acknowledged that there have been specific instances where gene therapy has shown **limited success**, such as in cases cited by Crystal where a vector expressing a specific gene product is directly transferred to diseased cells that do not express the gene product. A specific example cited by Crystal involves treating cystic fibrosis (CF) patients by administering a vector that expresses the cystic fibrosis transmembrane conductance regulator (CFTR) directly to cells that do not express CFTR. The results indicated that CFTR expression lasted "at least 9 days"; however, the therapeutic benefit is not reported in Crystal (see Crystal page 406 second and third columns). It is respectfully pointed out that the CFTR case differs from the instant case because the CFTR involves directly administering a vector that expresses a specific gene (CFTR) to diseased cells which do not express that gene. In the instant case, in

order to be able to practice the claimed method one of skill in the art would have to know which gene would express a protein that reduces or eliminates p21 expression in kidney cells. The specification does not describe any genes which encode proteins that reduce or eliminate p21 expression in kidney cells. Furthermore, the specification does not provide guidance on how to administer the gene such that the gene is expressed specifically in the targeted cells, at an appropriate level and for a sufficient period of time to result in the desired outcome.

Regarding antisense therapy, the Appellant quotes Branch (TIBS 23:45-50 (1998)) as acknowledging "advances in the field of antisense therapy: Today's peak specificity, whatever it is, will almost certainly rise as current strategies are optimized and advances in nucleic acid chemistry bring derivatives with fewer side effects" (See page 12 of the Appeal Brief, which cites page 47, second column, end of first full paragraph of Branch).

In response, it is noted that Branch clearly indicates a number of problems associated with antisense therapy which need to be addressed. As was indicated in a previous Office Action (see Non-Final Rejection Paper No. 7, mailed 8/15/02 page 5), Branch teaches (see the reference titled "A good antisense molecule is hard to find" TIBS: February 1998, p. 45-50):

> "Antisense molecules and ribozymes capture the imagination with their rational drug design and exquisite specificity. However, they are far more difficult to produce than originally anticipated, and **their ability to eliminate the function of a single gene has never been proven**. Furthermore, a wide variety of non-antisense effects have come to light." (Emphasis added by Examiner; See Branch, p. 45, abstract)

It is pointed out that the claims are specifically drawn to methods of reducing or eliminating p21 expression in kidney cells. However, Branch teaches that antisense molecules have never been proven to eliminate the function of a single gene. Furthermore, Branch also teaches, "Because non-antisense effects are not currently predictable, rules for rational design

cannot be applied to the production of non-antisense drugs. These effects must be explored on a case-by-case basis." (See Branch p. 50, first column). Therefore, antisense therapy is unpredictable without clear evidence of a specific antisense molecule's effectiveness in vivo. It is respectfully pointed out that the specification lacks evidence indicating the effectiveness of any antisense to reduce or eliminate p21 expression in a kidney, in vivo.

Additionally, it is pointed out that the claims encompass treating or preventing any pathophysiological state of the kidney by preventing or eliminating p21 expression in said kidney, which encompasses suppressing kidney transplant rejection as explicitly contemplated in the specification (e.g., see page 5, second paragraph and page 9, lines 5-6 of the specification). However, as indicated in a previous Office Action (see Non-Final Rejection Paper No. 7, mailed 8/15/02, page 6), Khanna et al. (Transplantation, Vol. 67: 1262-1268, 1999) teaches that cyclosporine, an immunosuppressive drug used to prevent organ transplant rejection, induces the expression of p21 (e.g., see Khanna p. 1264, Figure 2). Khanna also teaches, should p21 induction be a viable immunosuppressive strategy, inducing this molecule independent from the fibrogenic cytokine TGF-beta might reduce the toxicity associated with current immunosuppression." (See Khanna p. 1262, Abstract). Thus, Khanna indicates that p21 induction is associated with the immunosuppressive effects of the organ transplant rejection drug cyclosporine and induction of p21 may be a viable immunosuppressive strategy. The instant invention encompasses eliminating p21 gene expression for the therapeutic treatment of organ rejection, a notion that is in direct contradiction with the teaching of Khanna. Considering the closest prior art (Khanna) teaches that increasing p21 expression in transplanted organs may result in suppression of transplant rejection, it is highly unlikely, absent evidence to the contrary,

that reduction or elimination of p21 expression in a transplanted kidney would result in suppression of transplant rejection. The instant specification does not disclose any evidence which would indicate that reducing or eliminating p21 expression in transplanted kidneys would suppress transplant rejection. Therefore, the specification has not described to one of skill in the art how to treat or prevent the pathophysiological state that is kidney transplant rejection by reducing or eliminating p21 expression in the transplanted kidney.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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